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(54) Novel peptidase inhibitors.

(57) This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by H, or a substituted malonyl moiety. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

EP 0 364 344 A2

NOVEL PEPTIDASE INHIBITORS

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by H, or a substituted malonyl moiety. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to derivatives of certain peptidase substrates which are useful in inhibiting serine-, thio-, and metallo-dependent protease enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

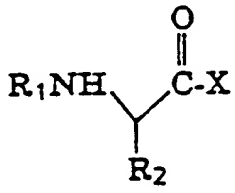
Still more specifically, this invention relates to derivatives of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

I. Serine Dependent Enzymes: These include such enzymes as Elastase (human leukocyte), Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin, β-Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and Kallikreins.

II. Thiol Dependent Enzymes: Cathepsin B and Calpain.

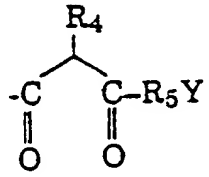
III.Metallo Dependent Enzymes: These include Enkephalinase, Pseudomonas Elastase and Leucine Aminopeptidase.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula



I

the hydrates, isosteres or the pharmaceutically acceptable salts thereof wherein X is



R_1 is hydrogen, an amino protecting group selected from Group K,an α-amino acid or a peptide comprised of a number of α-amino acid building blocks, said α-amino acid or peptide optionally bearing on its terminal nitrogen atom an amino protecting group selected from Group K,

R_2 is the "R group" residue of the α-amino acid responsible for directing the inhibitor to the active site of the enzyme or is -A-$SiR_7R_8R_9$, C_{1-10} alkyl, aralkyl or aryl with R_7, R_8 and R_9, each being selected from C_{1-10} alkyl, aralkyl or aryl and A is a C_{1-6} alkylene,

R_4 is the specific R-group residue of the α-amino acid for that peptidase substrate analog,

R_5 is an α-amino acid or peptide comprised of α-amino acids or is deleted,

Y is NHR_3 or OR_3 with R_3 being H, C_{1-7} alkyl, benzyl or phenethyl.

Unless otherwise stated the α-amino acids of the foregoing peptidase substrates are preferably in their L-configuration. A compound of this invention may be in free form, e.g. amphoteric form, or a salt form, e.g., acid addition or anionic salt. A compound may be converted into its salt or base form in an art-known manner, one from another. Preferred salts are trifluoroacetate, hydrochloride, sodium, potassium or ammonium salts, although the scope of salts embraced herein is not limited thereto, the scope being extended to include all of the salts known to be used in the art of peptide chemistry.

As used herein the term "alkyl" include the straight, branched-chain and cyclized manifestations

thereof, particularly such moieties as methyl, ethyl, n-butyl, t-butyl, cyclopropyl, n-propyl, pentyl, cyclopentyl, n-hexyl, cyclohexyl and cyclohexylmethyl. The term "aralkyl" includes those aryl moieties attached to a C_{1-4} alkylene. The term "aryl" within the definitions of R_2 includes both carbocyclic and heterocyclic moieties. Preferred aralykl and aryl moieties are phenyl, benzyl, naphthylmethyl, phenethyl, 2-pyridylmethyl, indolyl, pyridyl, indazolyl, furyl and thienyl are preferred. Other carbocyclics are such fused aryl moieties as pentalenyl, indenyl, naphthalenyl, naphthylmethyl, azulenyl, heptalenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl, anthracenyl, acephenanthrylenyl, aceanthrylenyl, triphenylenyl, pyrenyl, chrysenyl and naphthacenyl. In the term "-A-$SiR_7R_8R_9$" the alkylene moiety (i.e. "A") is a straight of branched-chain C_{1-7} alkylene moiety separating the "$SiR_7R_8R_9$" moiety from the carbon atom to which the "-A-$SiR_7R_8R_9$" radical is attached. Of the R_7, R_8 and R_9 radicals attached to the silicone atom it is preferred that two or three of these radicals be a C_{1-7} lower alkyl radical (preferably methyl or ethyl) and that when one of them contains an aryl radical it is preferred that that radical be a benzyl radical. It is preferred that the alkylene moiety be methylene. Preferred moieties are trimethylsilyl methyl, triethylsilylmethyl, benzyldiethylsilylmethyl, benzyldimethylsilylmethyl, benzylethylmethylsilylmethyl, dimethyl (3-pyridylmethyl) silylmethyl, dimethyl-(3-indolylmethyl) silylmethyl, and the like.

Before further defining and/or illustrating the scope of the peptidase substrate inhibitors embraced by Formula I, it may be convenient to state some of the more basic concepts related to peptides. For example, except for proline, all of the α-amino acids found in proteins have, as a common denominator, a free carboxyl group and a free unsubstituted amino group on the α-carbon atom (in proline, since proline's α-amino group is substituted it is really an α-imino acid, but for convenience, it will also be spoken of as an α-amino group). Additionally, each α-amino acid has a characteristic "R-group", the R-group being the side-chain, or residue, attached to the α-carbon atom of the α-amino acid. For example, the R-group residue for glycine is hydrogen, for alanine it is methyl, for valine it would be isopropyl. (Thus, throughout this specification the R_2 and R_4 moiety is the residue R-group for each indicated α-amino acid or is another radical which may be defined for these sites for any given protease inhibitors). For the specific R-groups - or side chains - of the α-amino acids reference to A.L. Lehninger's text on Biochemistry (see particularly Chapter 4) would be helpful.

As a further convenience for defining the scope of the compounds embraced by the generic concept of Formula 1, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various α-amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of Formula 1. These groups are set forth in Table II and the recognized abbreviations for the α-amino acid blocks are set forth in Table I.

TABLE I

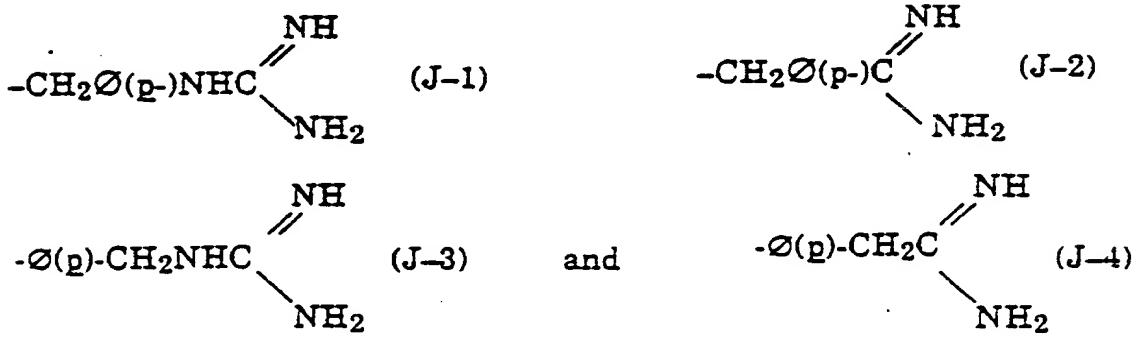
AMINO ACID	SYMBOL
Alanine	Ala
Arginine	Arg
Aspargine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	n-Val
Norleucine	n-Leu
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind
Sarcosin	Sar

TABLE II

Group A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives
C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives
D: Pro, Ind
E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, β-Valine, β-Alanine, n-Leu and n-methyl derivatives (β-representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives
F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.
G: Gly, Sar
G′: Gly

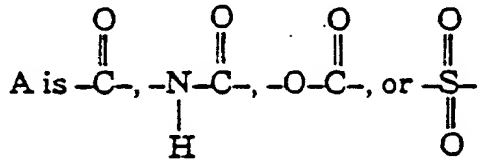
J:



with Ø, of course, representing phenyl (it being understood that the bond of J1-4 is always attached to the carbon atom of the involved amino acid as is, for example, the R_2 residues of the involved P_1-position amino acid).

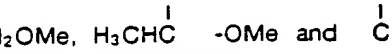
K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′

K′: A-Rz wherein



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

In those instances wherein the normal R-group residue of an α-amino acid contains an -OH radical (e.g. serine, threonine and tyrosine), it is to be understood that such radical can be derivatized. For example, in each of the foregoing instances the -OH radical can be converted to an ether. When so converted, such as for example to their methyl ethers, then such radicals will be referred to as O-methyl Ser, O-methyl Thr and O-methyl Tyr, respectively. These methyl ether radicals may also be depicted as

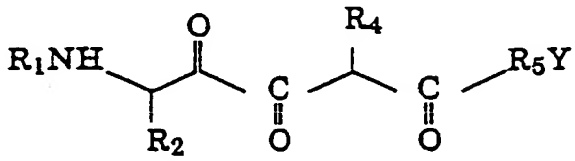


respectively. Similarly, other type derivatives will be analogously represented.

In those instances wherein Group K represents an -A-Rz moiety, it is preferred that A represent -C-(=O)- and that Rz represent acylsulfonamido, particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen. The preferred -A-Rz moieties being 4-[(4-chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl, 4-[(4-bromophenyl)sulfonylaminocarbonyl]-phenylcarbonyl and 4-[phenylsulfonylaminocarbonyl]phenylcarbonyl (said moieties being abbreviated as 4-Cl Ø-SAC-Bz, 4-Br Ø-SAC-Bz and Ø-SAC-Bz, respectively).

Quite obviously the modifications to the scissile amide bond of the peptidase substrates of this invention presents certain nomenclature difficulties. In order to maintain a general consistency throughout this application the following explanations are offered to obviate any ambiguities relating to the scope and intent of this invention.

In those instances wherein the compounds are defined by the formula



the R_2 moiety is the residue of the α-amino (or other defined moiety) located at the P_1 position, R_1 is either a protecting group moiety from the defined Group K, or is an α-amino acid or peptide moiety (having up to 4 α-amino acids). In defining the R_1 moiety for each specific enzyme, the amino acid or the amino acid of the peptide will be defined according to the P-position it occupies. For example, an R_1 peptide having 2 amino acids will consist of P_2-P_3 moieties, one having 3 amino acids will consist of P_2-P_3-P_4 moieties while one having 4 amino acids will consist of P_2-P_3-P_4-P_5 moieties. In all such instances the terminal nitrogen atom of such moieties may optionally bear a protecting group from the defined K group which, of course, includes the -A-Rz moiety. In defining the specific R_1 moieties for each of the individual protease enzyme inhibitors involved in this invention R_1 will, for example, define a P_2P_3 moiety bearing the Group K protecting group as $P_2P_3P_g$, P_g representing a protecting group of Group K on its terminal amine. If the terminal α-amino acid does not bear a protecting group it would then be represented as P_2P_3. In those instances wherein R_5 is a peptide, each α-amino acid will (when appropriate) be numbered sequentially (i.e., R_{5-1}, R_{5-2}, R_{5-3}, etc), and Y will be designated as the terminus of the substrate. In practice, it is preferred that the R_5 moiety contain no more than 3 amino acid units. For example, assume R_1 is a peptide containing two amino acids (Phe and Val) the terminal nitrogen atom of which bears a CBZ moiety, R_2 is the residue of the α-amino acid Arg, R_4 is the residue of the α-amino acid Leu, R_5 is the dipeptide consisting of two amino acids Ser and Val and Y is NHR_3 with R_3 being CH_3. That compound would be written as

CBZ-Phe-Val-Arg[C(O)Leu]-SerValNHCH$_3$.

The bracketed moiety (i.e.[C(O)Leu]) is used as an alert that the nitrogen atom of the P'_1 α-amino acid has been replaced by a carbonyl function, with Leu being the R_4 residue of that α-amino acid. Of course, it is also to be recognized that the bracketed moiety represents a malonyl moiety but for consistency and convenience it is preferred to designate that moiety as shown. The P'_2 and P'_3 moieties (i.e. SerVal) represent the R_5 moiety, Ser and Val may sometimes be referred to as R_{5-1} and R_{5-2}, respectively, with $NHCH_3$ representing the Y group at the terminal portion of the substrate. If R_5 were deleted and Y were OH or OCH_3, the compounds would be written as CBZ-Phe-Val-Arg[C(O)Leu]OH or CBZ-Phe-Val-Arg[C(O)Leu]-OCH_3, respectively.

In the light of the foregoing, the compounds of this invention are peptidase inhibitors capable of inhibiting enzymes of the group consisting of Human leukocyte elastase, Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin, β-Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin, Kallikreins, Cathepsin B, Calpain, Retroviral proteases required for replication, Enkephalinase, Pseudomonas elastase and Leucine aminopeptidase and are defined as:

Peptidase inhibitors having the formulae

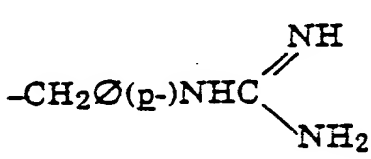
$$R_1NHCHR_2C(O)X \quad \text{and} \quad R_1NHCHR_2CH(OH)X \qquad \text{I}$$

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is -C(O)CHR$_4$C(O)R$_5$Y,

R_1 is H, an amino protecting group of Group K, an α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group or a peptide comprised of 2 to 4 α-amino acids,

the terminal amino acid of which bears a Group K protecting group,
R_2 is a residue of an α-amino acid, -A-$SiR_7R_8R_9$, C_{1-10} alkyl, aralkyl or aryl,
A is C_{1-6} alkylene and each of
R_7, R_8 and R_9 being C_{1-10} alkyl, aralkyl or aryl,
R_4 is a residue of an α-amino acid,
R_5 is an α-amino acid, a peptide comprised of 2 to 4 α-amino acids or is deleted,
Y is NHR_3 or OR_3 with
R_3 is H, C_{1-7} alkyl, benzyl or phenethyl,
the said protecting groups, α-amino acids or peptide moieties being selected from Groups A, B, C, D, E, F, G, J, C′, E′, F′, G′ and K, said groups being:
A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and their N-methyl derivatives
C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives
D: Pro, Ind
E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, n-Leu and their methyl derivatives
E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and their N-methyl derivatives
F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.
G: Gly, Sar
G′: Gly
J:



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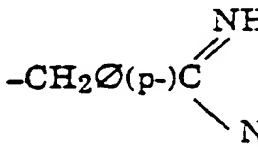

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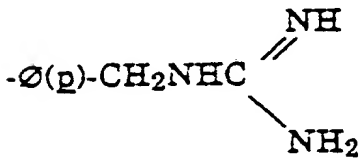

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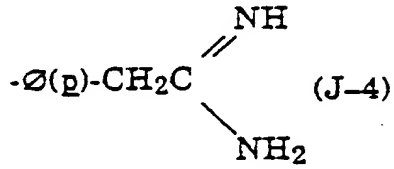
and



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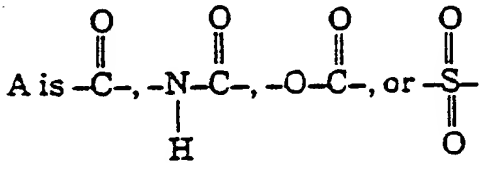
K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′
K′: A-Rz wherein



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

Compounds of Formula I which are useful as inhibitors of human leukocyte elastase are compounds of

the formula

$R_1NHCHR_2C(O)X$ Ia

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably methoxysuccinyl,

P_2 is an α-amino acid of Groups D and E, preferably proline,

P_3 is an α-amino acid of Groups D, and E, preferably isoleucine,

P_4 is deleted or is an α-amino acid of Group E, preferably alanine,

R_2 is the residue of an α-amino acid of Groups E and G, preferably nor-valine or valine,

R_4 is the residue of an α-amino acid of Groups E and G, preferably alanine,

R_5 is an α-amino acid of Groups E and G, preferably alanine, and

Y is NH_2.

Human leucocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of formula (Ia) have an antiinflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) is readily ascertained by standard biochemical technique well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg.body per day being useful for the aforementioned disease states. The preferred compounds for this enzyme are:

MeOSuc-Ala-Ile-Pro-Val[C(O)-Ala]Ala-NH_2,

MeOSuc-Ala-Ala-Pro-Val[C(O)-Ala]Ala-NH_2

[αN-($AdSO_2$)]-[εN-(2-CBz)]-Lys-Pro-Val-[C(O)-Ala]AlaNH_2,

[αN-($AdSO_2$)]-[εN-(2-CBz)]-Lys-Pro-Val-H.

Compounds of formula I which are useful as inhibitors of Cathepsin G are compounds of the formula

$R_1NHCHR_2C(O)X$ Ib

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably Suc, MeOSuc, Boc, 4-ClØSac-Bz or 4-BrØSac-Bz,

P_2 is an α-amino acid of Groups D, E or G,

P_3 is deleted or is an α-amino acid of Groups E or G, preferably Ala,

P_4 is deleted or is an α-amino acid of Groups E or G, preferably Ala,

R_2 is the residue of an α-amino acid of Groups E or F, preferably Phe,

R_4 is the residue of an α-amino acid of Groups E or G, preferably Ala, and

Y is NH_2 or OH.

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leucocyte inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infestations caused by infections in the lung. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend on the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compound of formula Ib is:

Suc-Ala-Ala-Pro-Phe-[C(O)Ala]OH.

Compounds of Formula I which are useful as inhibitors of thrombin are compounds of the formula

$R_1NHCHR_2C(O)X$ Ic

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is a Group K protecting group, (a) P_2P_3 or $P_2P_3P_g$ or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably DNS, Ts, J-1, 4-ClØSac-Bz or 4-BrØSac-Bz,

(a) P_2 is an α-amino acid of Groups D, E or F, preferably Pro,

P_3 is an α-amino acid of Group F, preferably in its D-configuration, preferably D-Phe,

(b) P_2 is an α-amino acid of Group E, preferably Ala,

P_3 is an α-amino acid of Groups C, E or G, preferably Ser,

P_4 is deleted or is an α-amino acid of Groups E, F or G, preferably Phe,

R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg,

R_4 is the residue of an α-amino acid of Groups C or G, preferably Gly or Ser,
R_5 is deleted or is an α-amino acid of Groups D or E, preferably Gly, and
Y is OH.

The compounds embraced by formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compound is as expressed for Cathepsin G and also includes:
Bz-J1-[C(O)Gly]Pro-OH.

Compounds of Formula I which are useful as inhibitors of chymotrypsin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Id**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is a group K protecting group, $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably the protecting group is Bz, Boc, 4-ClØSac-Bz, 4-BrØSac-Bz or ØSac-Bz,
P_2 is deleted or is an α-amino acid of Groups D, E or G, preferably Ala,
P_3 is deleted or is an α-amino acid of Groups E or G, preferably Ala,
P_4 is deleted or is an α-amino acid of Groups E or G, preferably Ala,
R_2 is an α-amino acid of Groups E and F, preferably Gly or Ala, and
Y is OH.

The end-use application of the compounds of (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state ofthe patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are as expressed for Cathepsin G and also include:
Pg-Phe-[C(O)Gly]Gly-OH,
Pg-Val-Pro-Phe-[C(O)Gly]Gly-OH,
Pg-Ala-Ala-Phe-[C(O)Gly]Gly-OH.
(In each instance Pg represents Bz, Boc, 4-Cl or 4-BrØSACBz, or ØSACBz.)

Compounds of Formula I which are useful as inhibitors of trypsin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ie**

the hydrates, isosteres of the pharmaceutically acceptable salts thereof, wherein
X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is a Group K protecting group, or (a) P_2P_3 or $P_2P_3P_g$, or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably the protecting group is DNS or Ts,
(a) P_2 is an α-amino acid of Groups D, E or F, preferably Pro or Ala,
P_3 is an α-amino acid of Groups F, preferably in the D-configuration, preferably D-Phe,
(b) P_2 is an α-amino acid of Groups D or E, preferably Pro or Ala,
P_3 is an α-amino acid of Groups C, G or E, preferably Ser,
P_4 is deleted or is an α-amino acid of Groups E or G, preferably Phe,
R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg,
R_4 is the residue of an α-amino acid of Groups C or G, preferably Gly or Ser,
R_5 is deleted or is an α-amino acid of Groups D, E or G, preferably Gly, and
Y is OH.

The end-use application of the compounds (Ie) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ie) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds useful for inhibiting trypsin

are the same for the inhibition of thrombin.

Compounds of Formula I which are useful as inhibitors of Cl-esterase are compounds of the formula

$R_1NHCHR_2C(O)X$ Ig

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2 or P_2P_g, P_g being a Group K protecting group, preferably CBZ,

P_2 is an α-amino acid of Groups A, B, C, D, E or G, preferably Ala,

R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg,

R_3 is H, C_{1-7} alkyl, benzyl or phenethyl,

R_4 is the residue of an α-amino acid of Group E, preferably Ala,

R_5 is an α-amino acid of Group E or is deleted, and

Y is NHR_3 or OR_3, preferably NH_2.

The compounds embraced by Formula (Ig) inhibit C_1-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ig) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compound is:

CBZ-Ala-(p-gua)-Phe-[C(O)Ala]NH_2.

Compounds of Formula I which are useful as inhibitors of C_3-convertase are compounds of the formula

$R_1NHCHR_2C(O)X$ Ih

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably Bz,

P_2 is an α-amino acid of Groups E or F, preferably Ala,

P_3 is an α-amino-acid of Groups E or F, preferably Leu,

R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg,

R_3 is H, C_{1-7} alkyl, benzyl, phenethyl, preferably H and benzyl,

R_4 is the residue of an α-amino acid of Group E, preferably Ala,

R_5 is an α-amino acid or is deleted, preferably it is deleted,

Y is OR_3 or NHR_3, preferably OR_3.

The compounds embraced by formula (Ih) inhibit C_3-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ih) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds are:

Bz-Leu-Ala-Arg[C(O)-Ala]$OCH_2Ø$,

Bz-Leu-Ala-Arg[C(O)-Ala]OH.

Compounds of Formula I which are useful as inhibitors of Urokinase are compounds of the formula

$R_1NHCHR_2C(O)X$ Ii

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably R_1 is P_2P_3, but when present P_g preferably is CSZ,

P_2 is an α-amino acid of Groups E or G, preferably Ala or Gly,

P_3 is an α-amino acid of Group B, preferably Glu,

R_2 is a residue of an α-amino acid of Groups A or J, preferably Arg or p-guanidino Phe (i.e. J-1),

R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,

R_4 is the residue of an α-amino acid of Group E, preferably Ala,

R_5 is an α-amino acid of Group E, preferably Ala, and

Y is OR_3 or NHR_3, preferably NH_2.

Preferred Urokinase inhibitors are:

H-Glu-Gly-Arg[C(O)Ala]AlaNH_2,

H-Glu-Gly-(p-gua)Phe-[C(O)Ala]AlaNH_2,

(p-gua) being para-guanidino.

The compounds of Formula (Ii) inhibit urokinase and therefore are useful in treating excessive cell growth disease state. As such the compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ii) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of plasminogen activator are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ij**

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably DNS,

P_2 is an α-amino acid of Groups G, preferably DNS,

P_3 is an α-amino acid of Groups B, preferably Glu,

R_2 is a residue of an α-amino acid of Groups A or J, preferably Arg or p-guanidino Phe (i.e., J-1,

R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,

R_4 is a residue of an α-amino acid of Group E, preferably Ala,

R_5 is an α-amino acid of Group E, preferably Ala, and

Y is OR_3 or NHR_3, preferably NH_2.

The preferred compound is:

DNS-Glu-Gly-(p-gua)Phe-[C(O)Ala]Ala-NH_2.

The compounds of the Formula (Ij) inhibit plasminogen activator and therefore are useful in treating excessive cell growth disease states. As such the compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, in the treatment of psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ij) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of acrosin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ik**

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably Boc,

P_2 is an α-amino acid of Group E, preferably Leu,

P_3 is an α-amino acid of Group E, preferably Leu,

R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg or p-guanidino Phe (i.e., J-1),

R_4 is the residue of an α-amino acid of Group E, preferably Ala,

R_5 is an α-amino acid of Group E or is deleted, preferably Ala, and

Y is NH_2.

The preferred compound is:

Boc-Leu-Leu-(p-gua)Phe-[C(O)Ala]Ala-NH_2.

The compounds of the Formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ik) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of D-Ala-D-Ala Carboxypeptidase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Im**

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is P_2 or P_2P_g, P_g being a Group K protecting group, preferably Ac,

P_2 is an α-amino acid of Groups E, C, A or $N\epsilon$-Ac-Lys, preferably $N\epsilon$-Ac-Lys or Lys,

R_2 is the residue of D-Ala,
R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,
R_4 is the residue of D-Ala, and
Y is OR_3, preferably OH or OCH_3.

The preferred compounds are:
(Nα,ε)-di-Ac-Lys-D-Ala[C(O)-(D)-Ala]OH,
(Nα,ε)-di-Ac-Lys-D-Ala[C(O)-(D)-Ala]OMe.

The compounds embraced by Formula (Im) are antibacterial agents particularly useful against gram negative organisms. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Im) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Cathepsin B are compounds of the formula

$R_1NHCHR_2C(O)X$ In

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is (a) P_2 or P_2P_g, or (b) P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably CBZ for P_2P_g and Ac for $P_2P_3P_g$,
(a) P_2 is an α-amino acid of Groups E and F, preferably Phe,
(b) P_2 is an α-amino acid of Groups E and F, preferably Phe,
P_3 is an α-amino acid of Groups E and F, preferably Leu,
R_2 is a residue of an α-amino acid of Groups A, E, or a Group J moiety or OBzThr, preferably Arg,
R_4 is a residue of an α-amino acid of Group E, preferably Leu,
R_5 is an α-amino acid of Groups E, F or G, preferably Gly, and
Y is OH.

The preferred compounds are:
Ac-Leu-Leu-Arg[C(O)-Leu]Gly-OH,
CBZ-Phe-Arg[C(O)-Leu]Gly-OH,
CBZ-Phe-Thr(OBz)[C(O)-Leu]Gly-OH.

The compounds of Formula (In) inhibit Cathepsin B and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in treating benign prostate hypertrophy, prostatic carcinoma, in treating psoriasis and in their use as abortifacients. Additionally, the compounds of (In) are useful as feed additives for cattle. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of pepsin are compounds of the formulae

$R_1NHCHR_2C(O)X$

and Io

$R_1NHCHR_2CH(OH)X$

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably P_g is Iva,
P_2 is an α-amino acid of Groups E or F or, preferably Val,
P_3 is an α-amino acid of Groups E or F or is deleted, preferably Val,
R_2 is the residue of an α-amino acid of Groups E or F, preferably Leu,
R_4 is the residue of an α-amino acid of Groups E, F or G, preferably Gly,
R_5 is an α-amino acid of Groups E and F, preferably Ala, and
Y is $NHCH_2(CH_3)_2$ or $NHCH_2CH(CH_3)_2$.

The preferred compounds are:

Iva-Val-Leu[C(O)Gly]Ala-$NHCH_2CH_2CH(CH_3)_2$,
Iva-Val-Val-Leu[C(O)Gly]Ala-N(Me)Ala-$NHCH_2CH_2CH(CH_3)_2$,
Iva-Val-Val-Leu[C(O)Gly]Gly-N(Me)Ala-$NHCH_2CH_2CH(CH_3)_2$.

The compounds of Formula (Io) inhibit pepsin and therefore exert and antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Io) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Cathepsin D are compounds of the formula

$R_1NHCHR_2C(O)X$ Ip

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E or F, preferably Val,
P_3 is an α-amino acid of Groups E or F, preferably Val,
R_2 is the residue of an α-amino acid of Groups E and F, preferably Phe,
R_4 is the residue of an α-amino acid of Groups E and F, preferably Phe,
R_5 is an α-amino acid of Groups E or F, preferably Ala,
Y is $NH(CH_2)_2CH(CH_3)_2$, $NHCH_2CH(CH_3)_2$ or NH_2.

The preferred compounds are:
CBZ-Val-Val-Phe[C(O)Phe]Ala-NH_2,
CBZ-Val-Val-Phe-[C(O)Phe]Ala-$NH(CH_2)_2CH(CH_3)_2$,
CBZ-Val-Val-Phe-[C(O)Phe]Ala-$NHCH_2CH(CH_3)_2$.

As inhibitors of Cathepsin D the compounds of Formula (Ip) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of enkephalinase are compounds of the formula

$R_1NHCHR_2C(O)X$ Iq

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably R_1 is P_2P_3,
P_2 is Gly,
P_3 is an α-amino acid of Group F or is deleted, preferably Tyr,
R_2 is the residue of Gly,
R_4 is the residue of an α-amino acid of Groups E or F, preferably Phe,
R_5 is deleted or is an α-amino acid of Groups E or F, preferably Met, and
Y is NH_2 or OH, preferably OH when R_5 is an amino acid and NH_2 when R_4 is deleted.

The preferred compound is:
Tyr-Gly-Gly[C(O)Phe]MetOH.

The compounds of Formula (Iq) inhibit enkephalinase and are therefore useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iq) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Pseudomonas elastase are compounds of the formula

$R_1NHCHR_2C(O)X$ Ir

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2 or P_2P_g, P_g being a Group K protecting group, preferably MeOSuc,
P_2 is an amino acid of Group E, preferably Ala,

R_2 is the residue of an α-amino acid of Groups E or G, preferably Ala,
R_4 is the residue of an α-amino acid of Groups E or F, preferably Ile,
R_5 is an α-amino acid of Groups E and G, preferably Ala, and
Y is NH_2.

The preferred compounds is:
MeOSuc-Ala-Ala[C(O)-Ile]Ala-NH_2.

The compounds of Formula (Ir) inhibit Pseudomonas elastase and therefore are useful as antibacterial agents particularly useful against infections caused by pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of leucine amino peptidase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Is**

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is H,
R_2 is the residue of an α-amino acid of Groups A, B, E, F or J, preferably Phe, Leu, Glu, Arg, J-1,
R_4 is the residue of an α-amino acid of Groups A, B, C, D, E, F, G or J, preferably Ala,
R_5 is an α-amino acid of Group E, preferably Ala, and
Y is NH_2.

The preferred compound is :
H-Leu[C(O)Ala]AlaNH_2.

The compounds of Formula (Is) are inhibitors of leucine amino peptidase and therefore are useful as immunostimulants useful in conjunctive therapy in the treatment with other known anticancer agents. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Is) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of calpain and Cathepsin B are compounds of the formula

$R_1NHCHR_2C(O)X$ **Iu**

wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably the protecting groups are CBZ, Bz or Ac,
P_2 is an α-amino acid of Groups E or F, preferably Val, Ile, Ala or Pro,
P_3 is an α-amino acid of Groups B, E, F or is deleted, preferably P_3 is deleted or is Ile,
R_2 is H, a residue of α-amino acids of Groups E, F, J, naphthyl, C_{1-7} alkyl, benzyl, phenethyl, or A-$SiR_7R_8R_9$, R_7, R_8 and R_9 being C_{1-10} alkyl, phenyl, benzyl, phenethyl and A is C_{1-6} alkylene, preferably R_2 is cyclohexylmethyl, naphthyl, Phe or naphthyl,
R_3 is C_{1-6} alkyl, benzyl or phenethyl, preferably C_{1-6} alkyl,
R_4 is the residue of an α-amino acid of Groups C, E or H,
R_5 is deleted, and
Y is OR_3 or NHR_3.

By their inhibition of calpain and cathepsin B proteases the compounds of (Iu) will (a) have an effect on cell motility through the extracellular matrix rendering the compounds useful for treating cancer metastases; (b) have long term changes in regulatory proteins (e.g. down-regulation of protein kinase C and breakdown of the cytoskeleton causing secondary effects on platelet activation such as (for enhancing clot formation) leukocyte degranulation (for treating inflammation and immunological diseases, e.g. arthritis, emphysema, multiple sclerosis, and systemic lupus); (c) have a general intracellular proteolysis, particular muscle cells, causing secondary effect on ischemia/reperfusion cell death, thereby rendering the compounds useful for treating stroke and heart attacks; and (d) will aid in blocking the lysis of red blood cells rendering the compounds useful in the treatment of conditions associated with excessive hemolysis such as in Sickle cell anemia and in kidney dialysis. It is to be expected that the end-use application dose range will be about

0.01 to 10 mg per kg of body weight per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of retroviral proteases required for replication are compounds of the formula

$R_1NHCHR_2C(O)X$ Iv

wherein X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably Iva,

P_2 is an α-amino acid of Groups C′, E′, F′ and G′, preferably Asn, Gln or Ala,

P_3 is an α-amino acid of Groups C′, E′, F′ and G′, preferably Asn, Gln or Ser,

P_4 is an α-amino acid of Groups C′, β-Ala, β-Val, or is deleted, preferably Ser or Thr,

R_2 is a residue of an α-amino acid of Groups F′ or E, or cyclohexylmethyl, preferably Tyr, Phe or CHM,

R_3 is C_{1-6} alkyl, benzyl or phenethyl,

R_4 is a residue of an α-amino acid of Group E′ or Val,

R_5 is deleted, and

Y is OR_3 or NHR_3.

Preferred compounds of Formula (Iv) are:

Thr-Gln-Asn-Tyr-[C(O)Phe]OCH_3,

Thr-Gln-Asn-Phe-[C(O)Phe]OCH_3,

Thr-Leu-Asn-Tyr-[C(O)Phe]NH_2,

Thr-Leu-Asn-Phe-[C(O)Phe]OCH_3,

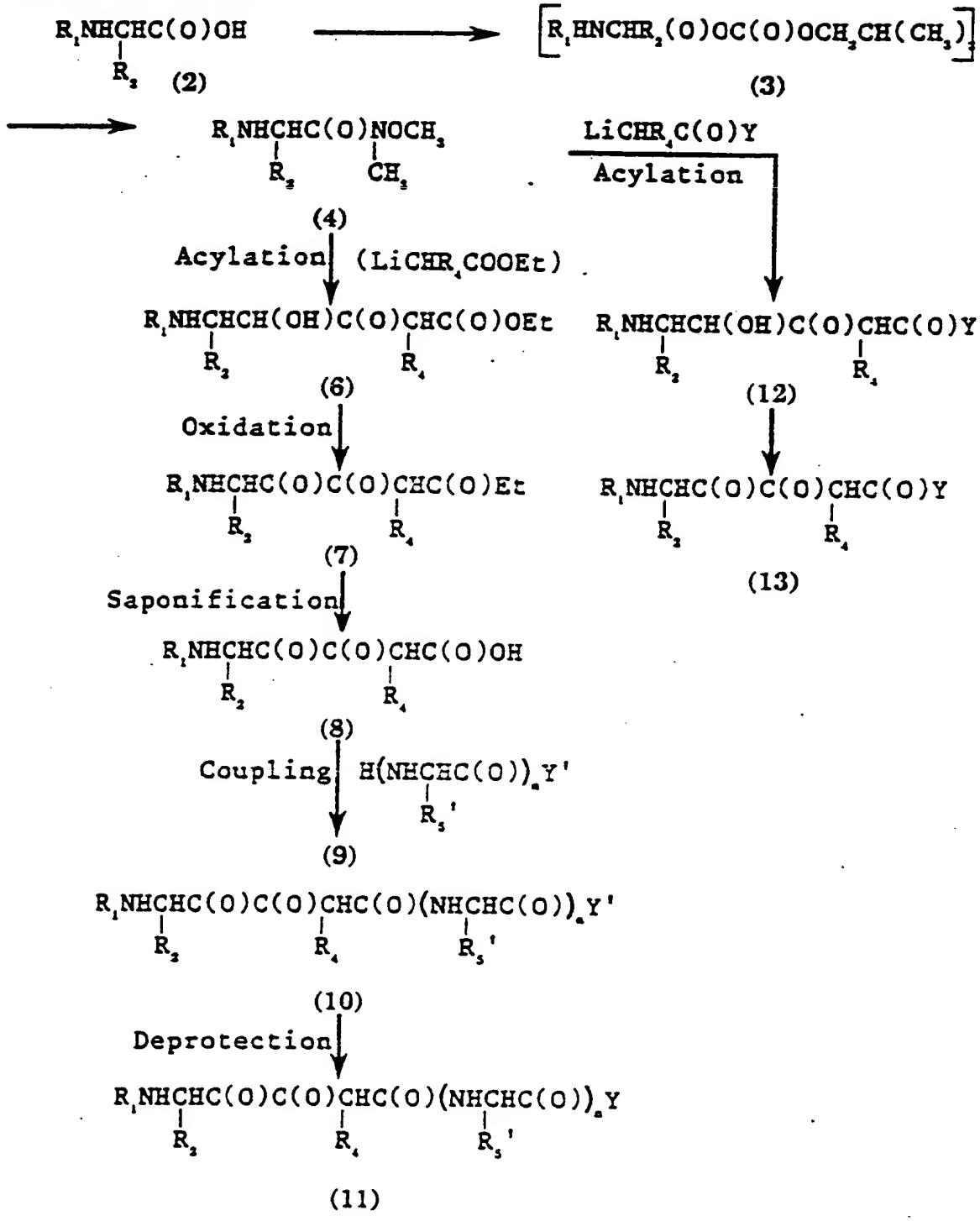
Iva-Ser-Asn-Phe-[C(O)Phe]OCH_3,

Iva-Ser-Asn-Phe-[C(O)Phe]NH_2.

In their end-use application in the treatment of retroviral infections, the compounds of Formula (Iv) will be administered at about 1-100 mg per kg of body weight per day, preferably intravenously.

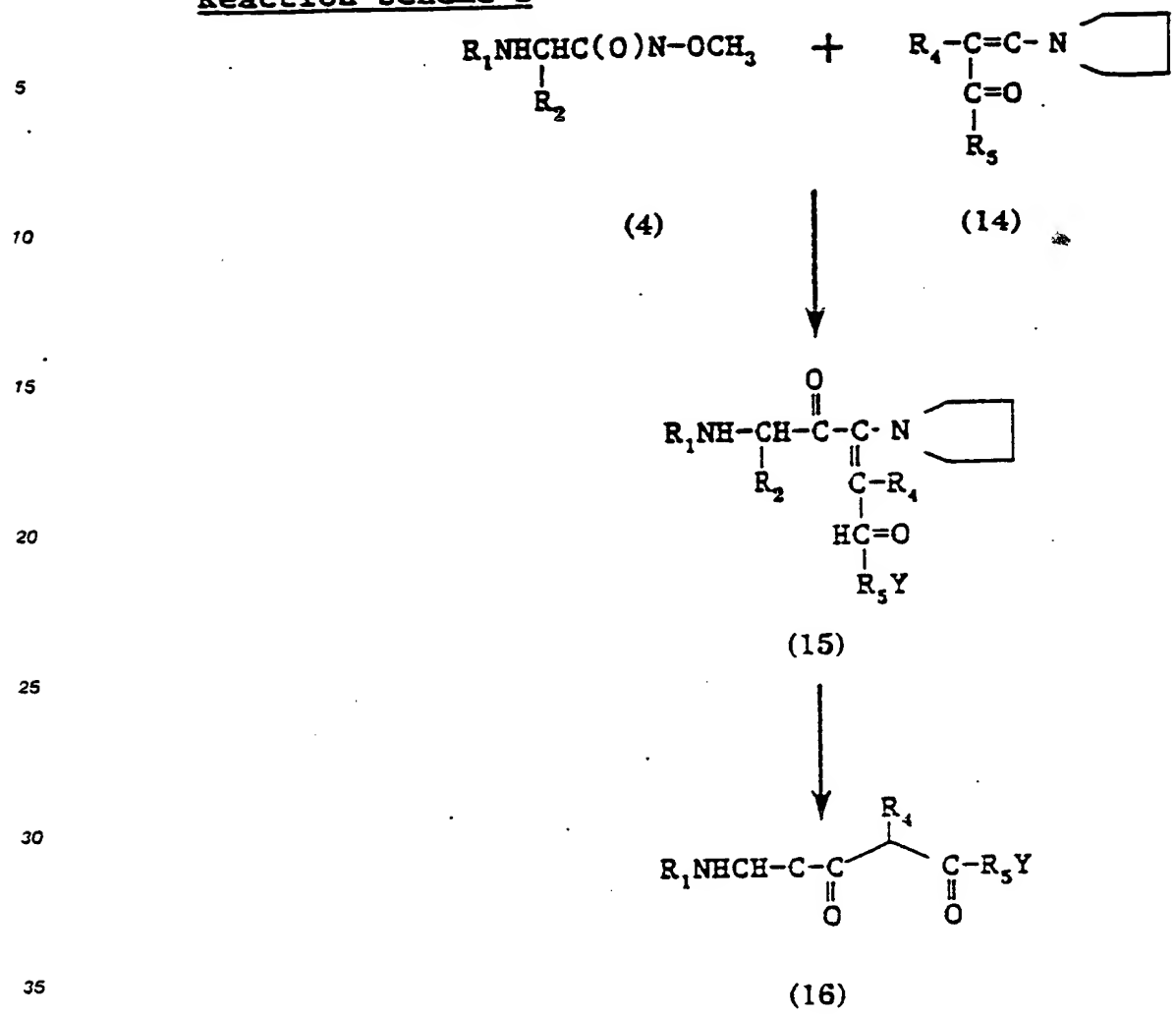
The preparation of the compounds of this invention may be effected by standard chemical processes analogously known in the art. The processes are depicted in Reaction Schemes A and B and described as follows:

Reaction Scheme A



wherein
Y' is NHR_3', or OR_3', P_g, alkyl, benzyl or phenethyl,
Y is NHR_3 or OR_3, R_3 being N, alkyl, benzyl or phenethyl,
R_5' is a residue of an amino acid,
n is 1 to 4 and R_1, R_2 and R_4 are as previously defined.

Reaction Scheme B



wherein

R_1, R_2, R_4, R_5 and Y are as previously defined.

In effecting the processes of the foregoing Reaction Scheme A, the starting materials (2) are subjected to process step (a) which is initiated by anionizing the starting material with a base, preferably N-methyl morpholine, triethylamine (TEA), diisopropylethylamine (DIEA) or other suitable amines. Preferably the anion is formed using excess quantities of the amine, stirring the mixture at about -15° C to 10° C, preferably 0° C. Addition of an equivalent amount of isobutylchloroformate with cooling at about -20° C forms an *in situ* mixed anhydride (3). (Other equivalently functioning peptide coupling agents, such as diethylcyanophosphonate, DCC, BOP reagents, BOP chloride, may be used in place of isobutylchloroformate.) Addition of molar equivalent amounts of N,O-dimethylhydroxylamine to the activated *in situ* intermediate (3) yields a dimethylhydroxamic acid derivative (i.e. an N-methyl-N-methoxy amide) of Formula 4. This coupling step is conducted under an inert atmosphere (argon or nitrogen) under anhydrous conditions.

The so-produced peptidyl α-hydroxy-N-methyl-N-methoxy amides of Formula (4) are acylated, using the alkyl lithio acetates of Formula (5), by standard acylation conditions such as by reaction of the amides (4) with the alkyl lithio derivatives (5) at about -78° C for about one hour and the resultant reaction mixture is allowed to warm to room temperature, following which the mixture is quenched by its addition to dilute hydrochloric acid to produce the desired intermediates of Formula (6). These hydroxy intermediates are subjected to oxidation procedures such as by use of (1) the Swern oxidation procedure, (2) a modified Jones reaction using pyridinium dichromate, (3) a chromic anhydride-pyridinium complex or (4) with 1,1,1-triacetoxy-2,1-benzoxidol.

In general the Swern oxidation is effected by reacting about 2 to 10 equivalents of dimethylsulfoxide (DMSO) with about 1 to 6 equivalents of trifluoromethylacetic anhydride [$(CF_3CO)_2O$] or oxalyl chloride [$-(COCl)_2$], said reactants being dissolved in an inert solvent, e.g., methylene chloride (CH_2Cl_2), said reactor being under an inert atmosphere (e.g., nitrogen or equivalently functioning inert gas) under anhydrous conditions at temperatures of about -80° C to -50° C to form an *in situ* sulfonium adduct to which is added about 1 equivalent of the alcohols of Formula (6). Preferably, the alcohols are dissolved in an inert solvent, e.g., CH_2Cl_2 or minimum amounts of DMSO, and the reaction mixture is allowed to warm to about -50° C (for about 10-20 minutes) and then the reaction is completed by adding about 3 to 10 equivalents of a tertiary amine, e.g., triethylamine, N-methyl morpholine, etc. Following oxidation the desired intermediates (7) are isolated and are ready for the next step of the reaction sequence.

In general, the modified Jones oxidation procedure may conveniently be effected by reacting the alcohols (6) with pyridinium dichromate by contacting the reactants together in a water-trapping molecular sieve powder, e.g., a grounded 3 Angström molecular sieve), wherein said contact is in the presence of glacial acetic acid at about 0° C to 50° C, preferably at room temperature.

Alternatively, 1 to 5 equivalents of a chromic anhydride-pyridine complex (i.e., a Sarett reagent prepared *in situ* (see Fieser and Fieser "Reagents for Organic Synthesis" Vol. 1, pp. 145 and Sarett, et al., J.A.C.S. 25, 422, (1953)) said complex being prepared *in situ* in an inert solvent (e.g., CH_2Cl_2) in an inert atmosphere under anhydrous conditions at 0° C to 50° C to which complex is added 1 equivalent of the alcohols (6) allow ing the reactants to interact for about 1 to 15 hours, followed by isolation of the desired product (7).

Another alternative process for converting the alcohols (6) to the desired ketones (7) is an oxidation reaction which employs periodane (i.e., 1,1,1-triacetoxy-2,1-benzoxiodol, (see Dess Martin, J. Org. Chem., 48, 4155, (1983)). This oxidation is effected by contacting about 1 equivalent of the alcohols (6) with 1 to 5 equivalents of periodane (preferably 1.5 equivalents), said reagent being in suspension in an inert solvent (e.g., methylene chloride) under an inert atmosphere (preferably nitrogen) under anhydrous conditions at 0° C to 50° C (preferably room temperature) and allowing the reactants to interact for about 1 to 48 hours.

Following oxidation and isolation, the acids of Formula (8) may be prepared by saponification procedures well known in the art, such as reaction of the esters with lithium hydroxide in a dioxane/water solvent mixture.

The products of Formula (9) may be obtained by coupling the acids (8) with the appropriate amine, using standard peptide coupling procedures using such coupling agents as isobutylchloroformate (and others as described above) according to procedures well known in the art. Following the coupling, the amino protecting groups may be selectively removed and the esters may be converted to their acids using standard procedures well known in the art.

The compounds of Formula (4) may also be converted to the desired malonyl derivatives wherein n is zero (i.e., R_5 is deleted) by acylation and oxidation procedures similar to those described above th produce compounds (12) and (13) respectively.

Alternatively, compounds of Formula (16) may be prepared by the reaction of Scheme B which essentially involves subjecting the hydroxamic derivatives of Formula (4) to a nucleophilic attack by an acylation with β-vinyl anion synton according to the techniques of R.R. Schmidt and J. Talbiershyl [Angen. Chem. Im. Ed. Engl. Vol. 15 (1976) No 3, page 171], which entails reaction of a β-acylenamine anion (14) (formed by treatment of the corresponding β-acylenamine with t-butyl lithium at temperatures below -100° C) with the hydroxomic derivatives (4) to produce compounds (15) which, upon sequention treatment with trifluoroacetic acid and water, form the desired compounds of Formula (16).

The solid phase sequential procedure can be performed using established automated methods such as by use of an automated peptide synthesizer. In this procedure an amino protected amino acid is bound to a resin support at the carboxy terminal end, the amino acid is deprotected at the amino position at which a peptide linkage is desired, the amino group neutralized with a base and the next amino protected amino acid in the desired sequence is coupled in a peptide linkage. The deprotection, neutralization and coupling steps are repeated until the desired polypeptide is synthesized. The compounds of the present invention are thus synthesized from their carboxy terminal end to their amino terminal end. The amino protected amino acid can be a conventional amino acid, a derivative or isomer thereof, or a spacer group. The resin support employed can be any suitable resin conventionally employed in the art for the solid phase preparation of polypeptides. The preferred resin is polystyrene which has been cross-linked with from about 0.5 to about 3% divinyl benzene, which has been either benzhydrylamidated, chloromethylated or hydroxymethylated to provide sites for amide or ester formation with the initially introduced amino protected amino acid.

An example of a hydroxymethyl resin is described by Bodansky et al. [Chem. Ind. (London) 38, 1597-98

(1966)]. The preparation of chloromethyl and benzhhydrylamine resins are described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Edition, Pierce Chemical Co., Rockford, Illinois (1984), Chapter 2, pp. 54-55]. Many of these resins are available commercially. In general, the amino protected amino acid which is desired on the carboxy-terminal end of the peptide is bound to the resin using standard procedures and practices as are well known and appreciated in the art. For example, the amino protected amino acid can be bound to the resin by the procedure of Gisin [Helv. Chem. Acta, 56, 1476 (1973)]. When it is desired to use a resin containing a benzhydrylamine moiety as the resin binding site an amino protected amino acid is coupled to the resin through an amide linkage between its α-carboxylic acid and the amino moiety of the resin. This coupling is effected using standard coupling procedures as described below. Many resin-bound amino acids are available commercially.

The α-amino protecting group employed with each amino acid introduced into the polypeptide sequence may be any such protecting group known in the art. Among the classes of amino protecting groups contemplated are: (1) acyl type protecting groups such as formyl, trifluoroacetyl, phthalyl, p-toluenesulfonyl (tosyl), benzenesulfonyl, nitrophenylsulfenyl, tritylsulfenyl, o-nitrophenoxyacetyl, and α-chlorobutyryl; (2) aromatic urethane type protecting groups such as benzyloxycarbonyl and substituted benzyloxycarbonyls such as p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 1-(p-biphenylyl)-1- methylethoxycarbonyl, α-, α-dimethyl-3,5-dimethoxybennzyloxycarbonyl, and benzyhydryloxycarbonyl; (3) aliphatic urethane protecting groups such as tert-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, and allyloxycarbonyl; (4) cycloalkyl urethane type protecting groups such as cyclopentyloxycarbonyl, adamantyloxycarbonyl, and cyclohexyloxycarbonyl; (5) thio urethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bzl); (7) trialkylsilane protecting groups such as trimethylsilane. The preferred α-amino protecting group is tert-butyloxycarbonyl (Boc). The use of Boc as an α-amino protecting group for amino acids is described by Bodansky et al. in "The Practice of Peptide Synthesis", Springer-Verlag, Berlin (1984), p. 20.

Following the coupling of the amino protected amino acid to the resin support, the α-amino protecting group is removed using any suitable procedure such as by using trifluoroacetic acid, trifluoroacetic acid in dichloromethane, or HCl in dioxane. The deprotection is carried out at a temperature of between 0 °C and room temperature. Other standard cleaving reagents may be used for removal of specific amino protecting groups under conditions well known and appreciated in the art.

After removal and neutralization of the α-amino protecting group the next desired amino-protected amino acid is coupled through a peptide linkage. This deprotection, neutralization and coupling procedure is repeated until a polypeptide of the desired sequence is obtained. Alternatively, multiple amino acid groups may be coupled by the solution method prior to coupling with the resin supported amino acid sequence.

The selection and use of an appropriate coupling reagent is within the skill of the ordinary practitioner in the art. Particularly suitable coupling reagents where the amino acid to be added is Gln, Asn, or Arg are N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The use of these reagents prevents nitrile and lactam formation. Other coupling agents are (1) carbodiimides (e.g., N,N-dicyclohexylcarbodiimide and N-ethyl-N′-(γ-dimethylaminopropylcarbodiimide); (3) ketenimines; (4) isoxazolium salts (e.g., N-ethyl-5-phenylisoxazolium-3-sulfonate); (5) monocyclic nitrogen containing heterocyclic amides of aromatic character containing one through four nitrogens in the ring such as imidazolides, pyrazolides, and 1,2,4-triazolides (specific heterocyclic amides that are useful include N,N-carbonyldiimidazole and N,N-carbonyl-di-1,2,4-triazole); (6) alkoxylated acetylene (e.g., ethoxyacetylene); (7) reagents which form a mixed anhydride with the carboxyl moiety of the amino acid (e.g., ethylchloroformate and isobutylchloroformate) or the the symmetrical anhydride of the amino acid to be coupled (e.g., Boc-Ala-o-Ala-Boc); (8) nitrogen containing heterocyclic compounds having a hydroxy group on one ring nitrogen (e.g., N-hydroxyphthalimide, N-hydroxysuccinimide, and 1-hydroxybenzotriazole). Other activating reagents and their use in peptide coupling are described by Kapoor [J. Pharm. Sci., 59, 1-27 (1970)]. The generally preferred coupling method for the amino acids used in the present invention is the use of the symmetrical anhydride as the coupling agent.

The preferred coupling method for Gln, Asn and Arg is to react the protected amino acid, or derivatives or isomers thereof, with N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (1:1) in N,N-dimethylformamide (DMF) in the presence of the resin or resin-bound amino acid or peptide. The preferred coupling method for other amino acids involves reacting the protected amino acid, or derivative or isomer thereof, with N,N-dicyclohexylcarbodiimide in dichloromethane to form the symmetrical anhydride. The symmetrical anhydride is then introduced into the solid phase reactor containing the resin or resin-bound amino acid or peptide, and the coupling is carried out in a medium of (DMF), or dichloromethane, or DMF: dichloromethane (1:1). A medium of DMF is preferred. The success of the coupling reaction at each stage of

the synthesis is monitored by a ninhydrin test as described by Kaiser et al. [Analyt. Biochem. 34, 595 (1970)]. In cases where incomplete coupling occurs, the coupling procedure is repeated. If the coupling is still incomplete, the deprotected amine is capped with a suitable capping reagent to prevent its continued synthesis. Suitable capping reagents and the use thereof are well known and appreciated in the art. Examples of suitable capping reagents are acetic anhydride and acetylimidazole as described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Ed., Pierce Chemical Co., Rockford, Ill. (1984), Chapter 2, p. 73].

After the desired amino acid sequence has been obtained, the peptide is cleaved from the resin. This can be effected by procedures which are well known and appreciated in the art, such as by hydrolysis of the ester or amide linkage to the resin. It is preferred to cleave the peptide from the benzhydrylamine resin with a solution of dimethyl sulfide, p-cresol, thiocresol, or anisole in anhydrous hydrogen fluoride. The cleavage reaction is preferably carried out at temperatures between about 0° C and about room temperature, and is allowed to continue preferably from between about 5 minutes to about 5 hours.

As is known in the art of solid phase peptide synthesis, many of the amino acids bear side chain functionalities requiring protecting during the preparation of the peptide. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bzl), or t-butylsulfonyl moieties can be used to protect the sulfide containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl (Bzl) or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl (Bzl) ether can be used to protect the hydroxy containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (2Br-Z) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

The following specific examples are given to illustrate the preparation of this invention although the scope of compounds is meant to be limiting to the scope of compounds embraced by formula I.

EXAMPLE 1

4-Hydroxy-6-phenyl-5-[((phenylmethoxy)carbonyl)amino]-3-oxohexanoic Acid Ethyl Ester

A solution of 2-hydroxy-4-phenyl-3-[((phenylmethoxy)carbonyl)amino]butanoic acid, N-methoxy-N-methylamide (372 mg, 1.0 mmol) in tetrahydrofuran is cooled to -78° C and ethyl lithioacetate (72 mg, 3.0 mmol) is added. The solution is stirred at -78° C for 1 hour, allowed to warm to room temperature, stirred for 1 hour and poured into dilute HCl. The product is extracted by ethyl acetate (3 x 150 ml) and the combined organic extracts are washed with $NaHCO_3$, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product is purified by flash chromatography on silica gel.

EXAMPLE 2

3,4-Dioxo-5-[((phenylmethoxy)carbonyl)amino]-6-phenylhexanoic Acid Ethyl Ester

A solution of 4-hydroxy-6-phenyl-5-[((phenylmethoxy)carbonyl)amino]-3-oxohexanoic acid ethyl ester (397 mg, 1.0 mmol) is dissolved in acetonitrile (15 ml) and the Dess-Martin periodinane (1.27 g, 3.0 mmol)) is added. To the mixture trifluoroacetic acid (342 mg, 3.0 mmol) is added and the mixture is stirred for 48 h. The solvent is removed *in vacuo* and EtOAc (100 ml) is added, followed by the addition of a solution of $NaHCO_3$ (0.80 g) and $Na_2S_2O_3$ (1.41 g) in H_2O (25 ml). The organic layer is separated and the aqueous phase extracted with ethyl acetate. The combined extracts are dried over $Na_2S_2O_3$ and the solvent is removed *in vacuo*. The product is purified by flash chromatography on silica gel.

EXAMPLE 3

3,4-Dioxo-5-[((phenylmethoxy)carbonyl)amino]-6-phenylhexanoic Acid

To a solution of 3,4-dioxo-5-[((phenylmethoxy)carbonyl)amino]-6-phenylhexanoic acid ethyl ester (400 mg, 1.0 mmol) in dioxane/H_2O (10:1), lithium hydroxide (72 mg, 3.0 mmol) is added. The mixture is stirred for 3 h, the solvents are removed *in vacuo* and the crude product is used without purification.

EXAMPLE 4

N-[3,4-Dioxo-5-(((phenylmethoxy)carbonyl)amino))-6-phenylhexanoyl]glycinamide

To a solution of 3,4-dioxo-5-[((phenylmethoxy)carbonyl)amino]-6-phenylhexanoic acid (370 mg, 1.0 mmol) in methylene chloride (300 ml) is added N-methylmorpholine (0.30 g, 3.0 mmol). The mixture is cooled to -15° C, and isobutylchloroformate (136 mg, 1.0 mmol) is added. The mixture is stirred at -15° C for 15 minutes followed by the addition of N,O-dimethylhydroxylamine hydrochloride (194 mg, 1.0 mmol). The mixture is stirred at -15° C for 1 hour, allowed to warm to room temperature, and stirred for 3 h. The reaction mixture is poured into H_2O (300 ml), and the aqueous phase is extracted with methylene chloride (2 x 150 ml). The combined organic extracts are dried over Na_2SO_4, reduced in volume to 100 ml, and filtered through silica gel (2 in.). The solvent is removed *in vacuo* to give the crude product which is purified by flash chromatography.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of the art procedures by which the compounds may be evaluated for their biochemical effects is also included herein.

For example, human elastase is assayed *in vitro* using chromophoric peptides, succinylalanylalanylalanyl-p-nitro-anilide, methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide, and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those described by Lottenberg et al. Enzyme is purified from human sputum, although recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot, whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison.

Similarly, the other proteases are assayed and effects of inhibitors are assessed *in vitro* by similar spectroscopic techniques: cathepsin G; thrombin; chymotrypsin; trypsin; plasmin; C1 esterase; urokinase; plasminogen activator; acrosin; β-lactamase; cathepsin B; pepsin; cathepsin D and leucine aminopeptidase. Pseudomonas elastase is measured in a coupled assay procedure using a human leastase substrate and microsomal aminopeptidase.

Radiometric assays of angiotensin I-converting enzyme and enkephalinase and their inhibitors are based on the procedure of Ryan and use tritiated substrate purchased from Ventrex Laboratories, Inc. Radioimmunoassay is used for studies with renin. C3-convertase is measured as described by Tack et al.

By following the technique referred above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are

preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 0.01-10 mg per kg of body weight per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, perservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc. or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

Claims

1. A compound of the formulae

$$R_1NHCHR_2C(O)X$$

and

$$R_1NHCHR_2CH(OH)X \qquad I$$

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is H, an amino protecting group of Group K, and α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group or a peptide comprised of 2 to 4 α-amino acids, the terminal amino acid of which bears a Group K protecting group,
R_2 is a residue of an α-amino acid, $-A-SiR_7R_8R_9$, C_{1-10} alkyl, aralkyl or aryl,
A is C_{1-6} alkylene and each of
R_7, R_8 and R_9 being C_{1-10} alkyl, aralykl or aryl,
R_4 is a residue of an α-amino acid,
R_5 is an α-amino acid, a peptide comprised of 2 to 4 α-amino acids or is deleted,
Y is NHR_3 or OR_3 with
R_3 is H, C_{1-7} alkyl, benzyl or phenethyl,
the said protecting groups, α-amino acids or peptide moieties being selected from Groups A, B, C, D, E, F,

G, J, C′, E′, F′, G′ and K, said groups being:

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and their N-methyl derivatives

C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, n-Leu and their methyl derivatives

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives

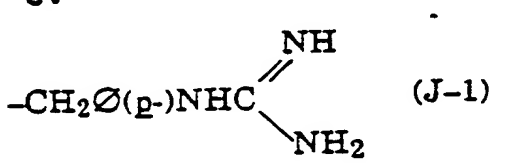
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and their N-methyl derivatives

F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.

G: Gly, Sar

G′: Gly

J:



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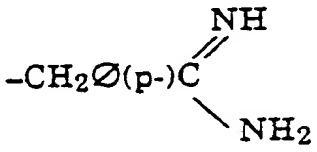

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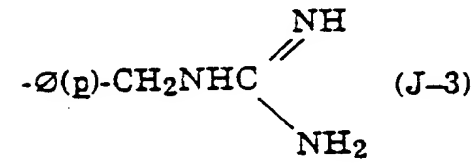

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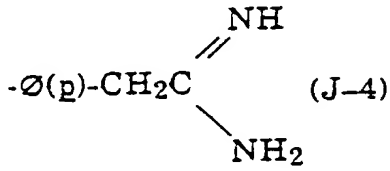
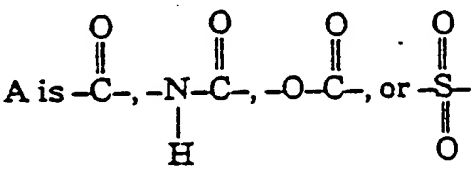


(J–4)

K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Iso valeryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′

K′: A-Rz wherein



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

2. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ Ia

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is $-C(O)CHR_4C(O)R_5Y$,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups D, E and F,

P_3 is an α-amino acid of Groups D and E,

P_4 is deleted or is an α-amino acid of Group E,

R_2 is the residue of an α-amino acid of Groups E and G,

R_4 is the residue of an α-amino acid of Groups E and G,

R_5 is an α-amino acid of Groups E and G, and
Y is NH_2.

3. A compound of Claim 2, said compound being
MeOSuc-Ala-Ile-Pro-Val[C(O)-Ala]Ala-NH_2,
MeOSuc-Ala-Ala-Pro-Val[C(O)-Ala]Ala-NH_2,
[αN-($AdSO_2$)]-[εN-(2-CBz)]-Lys-Pro-Val-[C(O)-Ala]AlaNH_2,
[αN-($AdSO_2$)]-[εN-(2-CBz)]-Lys-Pro-Val-H.

4. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ib**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is -$C(O)CHR_4C(O)R_5Y$,
R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups D, E or G,
P_3 is deleted or is an α-amino acid of Groups E or G,
P_4 is deleted or is an α-amino acid of Groups E or G,
R_2 is the residue of an α-amino acid of Groups E or F,
R_4 is the residue of an α-amino acid of Groups E or G, and
Y is NH_2 or OH.

5. A compound of Claim 4, said compound being
Suc-Ala-Ala-Pro-Phe-[C(O)Ala]OH.

6. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ic**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is-$C(O)CHR_4C(O)R_5Y$,
R_1 is a Group K protecting group, (a) P_2P_3 or $P_2P_3P_g$ or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
(a) P_2 is an α-amino acid of Groups D, E or F,
P_3 is an α-amino acid of Group F,
(b) P_2 is an α-amino acid of Group E,
P_3 is an α-amino acid of Groups C, E or G,
P_4 is deleted or is an α-amino acid of Groups E, F or G,
R_2 is the residue of an α-amino acid of Groups A or J,
R_4 is the residue of an α-amino acid of Groups C or G,
R_5 is deleted or is an α-amino acid of Groups D or E, and
Y is OH.

7. A compound of Claim 6, said compound being
Bz-J1-[C(O)Gly]Pro-OH.

8. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Id**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is -$C(O)CHR_4C(O)R_5Y$,
R_1 is a group K protecting group, $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
P_2 is deleted or is an α-amino acid of Groups D, E or G,
P_3 is deleted or is an α-amino acid of Groups E or G,
P_4 is deleted or is an α-amino acid of Groups E or G,
R_2 is an α-amino acid of Groups E and F, and
Y is OH.

9. A compound of Claim 8, said compound being
Pg-Phe-[C(O)Gly]Gly-OH,
Pg-Val-Pro-Phe-[C(O)Gly]Gly-OH,
Pg-Ala-Ala-Phe-[C(O)Gly]Gly-OH.
(In each instance Pg represents Bz, Boc, 4-Cl or 4-BrØSACBz, or ØSACBz.)

10. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ie**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is -$C(O)CHR_4C(O)R_5Y$,
R_1 is a Group K protecting group, or (a) P_2P_3 or $P_2P_3P_g$, or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,

(a) P_2 is an α-amino acid of Groups D, E or F,
P_3 is an α-amino acid of Groups F,
(b) P_2 is an α-amino acid of Groups D or E,
P_3 is an α-amino acid of Groups C, G or E,
P_4 is deleted or is an α-amino acid of Groups E or G,
R_2 is the residue of an α-amino acid of Groups A or J,
R_4 is the residue of an α-amino acid of Groups C or G,
R_5 is deleted or is an α-amino acid of Groups D, E or G, and
Y is OH.

11. A compound of Claim 10, said compound being
Bz-J1-[C(O)Gly]Pro-OH.

12. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ig**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2 or P_2P_g, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups A, B, C, D, E or G,
R_2 is the residue of an α-amino acid of Groups A or J,
R_3 is H, C_{1-7} alkyl, benzyl or phenethyl,
R_4 is the residue of an α-amino acid of Group E,
R_5 is an α-amino acid of Group E or is deleted, and
Y is NHR_3 or OR_3, preferably NH_2.

13. A compound of Claim 12, said compound being
CBZ-Ala-(p-gua)-Phe-[C(O)Ala]NH_2.

14. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ih**
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E or F,
P_3 is an α-amino acid of Groups E or F,
R_2 is the residue of an α-amino acid of Groups A or J,
R_3 is H, C_{1-7} alkyl, benzyl, phenethyl,
R_4 is the residue of an α-amino acid of Group E,
R_5 is an α-amino acid or is deleted,
Y is OR_3 or NHR_3.

15. A compound of Claim 14, said compound being
Bz-Leu-Ala-Arg[C(O)-Ala]$OCH_2Ø$,
Bz-Leu-Ala-Arg[C(O)-Ala]OH.

16. Compounds of claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ii**
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably R_1 is P_2P_3, but when present P_g preferably is CBZ,
P_2 is an α-amino acid of Groups E or G,
P_3 is an α-amino acid of Group B,
R_2 is a residue of an α-amino acid of Groups A or J,
R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,
R_4 is the residue of an α-amino acid of Group E,
R_5 is an α-amino acid of Group E, and
Y is OR_3 or NHR_3.

17. A compound of Claim 16, said compound being
H-Glu-Gly-Arg[C(O)Ala]$AlaNH_2$,
H-Gly-Glu-(p-gua)Phe-[C(O)Ala]$AlaNH_2$,
(p-gua) being para-guanidino.

18. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ij**
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups G,
P_3 is an α-amino acid of Groups B,
R_2 is a residue of an α-amino acid of Groups A or J,
R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,
R_4 is a residue of an α-amino acid of Group E,
R_5 is an α-amino acid of Group E, and
Y is OR_3 or NHR_3.

19. A compound of Claim 18, said compound being
DNS-Glu-Gly-(p-gua)Phe-[C(O)Ala]Ala-NH_2.

20. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ Ik
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Group E,
P_3 is an α-amino acid of Group E,
R_2 is the residue of an α-amino acid of Groups A or J,
R_4 is the residue of an α-amino acid of Group E,
R_5 is an α-amino acid of Group E or is deleted, and
Y is NH_2.

21. A compound of Claim 20, said compound being
Boc-Leu-Leu-(p-gua)Phe-[C(O)Ala]Ala-NH_2.

22. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ Im
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is P_2 or P_2P_g, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E, C, A or Nε-Ac-Lys,
R_2 is the residue of D-Ala,
R_3 is H, C_{1-6} alkyl, benzyl or phenethyl,
R_4 is the residue of D-Ala, and
Y is OR_3.

23. A compound of Claim 22, said compound being
(Nα,ε)-di-Ac-Lys-D-Ala[C(O)-(D)-Ala]OH,
(Nα,ε)-di-Ac-Lys-D-Ala[C(O)-(D)-Ala]OMe.

24. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ In
wherein X is $-C(O)CHR_4C(O)R_5Y$,
R_1 is (a) P_2 or P_2P_g, or (b) P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
(a) P_2 is an α-amino acid of Groups E and F,
(b) P_2 is an α-amino acid of Groups E and F,
P_3 is an α-amino acid of Groups E and F,
R_2 is a residue of an α-amino acid of Groups A, E, or a Group J moiety or OBzThr,
R_4 is a residue of an α-amino acid of Group E,
R_5 is an α-amino acid of Groups E, F or G, and
Y is OH.

25. A compound of Claim 24, said compound being
Ac-Leu-Leu-Arg[C(O)-Leu]Gly-OH,
CBZ-Phe-Arg[C(O)-Leu]Gly-OH,
CBZ-Phe-Thr(OBz)[C(O)-Leu]Gly-OH.

26. Compounds of Claim 1 of the formulae

$$R_1NHCHR_2C(O)X$$

and Io

$$R_1NHCHR_2CH(OH)X$$

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,
R$_1$ is P$_2$P$_3$ or P$_2$P$_3$P$_g$, P$_g$ being a Group K protecting group,
P$_2$ is an α-amino acid of Groups E or F,
P$_3$ is an α-amino acid of Groups E or F or is deleted,
R$_2$ is the residue of an α-amino acid of Groups E or F,
R$_4$ is the residue of an α-amino acid of Groups E, F or G,
R$_5$ is an α-amino acid of Groups E and F, and
Y is NHCH$_2$(CH$_3$)$_2$ or NHCH$_2$CH(CH$_3$)$_2$.

27. A compound of Claim 26, said compound being
Iva-Val-Leu[C(O)Gly]Ala-NHCH$_2$CH$_2$CH(CH$_3$)$_2$,
Iva-Val-Val-Leu[C(O)Gly]Ala-N(Me)Ala-NHCH$_2$CH$_2$CH(CH$_3$)$_2$,
Iva-Val-Val-Leu[C(O)Gly]Gly-N(Me)Ala-NHCH$_2$CH$_2$CH(CH$_3$)$_2$.

28. Compounds of Claim 1 of the formula

R$_1$NHCHR$_2$C(O)X **Ip**

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,
R$_1$ is P$_2$P$_3$ or P$_2$P$_3$P$_g$, P$_g$being a Group K protecting group,
P$_2$ is an α-amino acid of Groups E or F,
P$_3$ is an α-amino acid of Groups E or F,
R$_2$ is the residue of an α-amino acid of Groups E and F,
R$_4$ is the residue of an α-amino acid of Groups E and F,
R$_5$ is an α-amino acid of Groups E or F,
Y is NH(CH$_2$)$_2$CH(CH$_3$)$_2$, NHCH$_2$CH(CH$_3$)$_2$ or NH$_2$.

29. A compound of Claim 28, said compound being
CBZ-Val-Val-Phe-[C(O)Phe]Ala-NH$_2$,
CBZ-Val-Val-Phe-[C(O)Phe]Ala-NH(CH$_2$)$_2$CH(CH$_3$)$_2$,
CBZ-Val-Val-Phe-[C(O)Phe]Ala-NHCH$_2$CH(CH$_3$)$_2$.

30. Compounds of Claim 1 of the formula

R$_1$NHCHR$_2$C(O)X **Iq**

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,
R$_1$ is P$_2$P$_3$ or P$_2$P$_3$P$_g$, P$_g$ being a Group K protecting group, preferably R$_1$ is P$_2$P$_3$,
P$_2$ is Gly,
P$_3$ is an α-amino acid of Group F or is deleted,
R$_2$ is the residue of Gly,
R$_4$ is the residue of an α-amino acid of Groups E or F,
R$_5$ is deleted or is an α-amino acid of Groups E or F,, and
Y is NH$_2$ or OH.

31. A compound of Claim 30, said compound being
Tyr-Gly-Gly[C(O)Phe]MetOH.

32. Compounds of Claim 1 of the formula

R$_1$NHCHR$_2$C(O)X **Ir**

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,
R$_1$ is P$_2$ or P$_2$P$_g$, P$_g$ being a Group K protecting group,
P$_2$ is an amino acid of Group E,
R$_2$ is the residue of an α-amino acid of Groups E or G,
R$_4$ is the residue of an α-amino acid of Groups E or F,
R$_5$ is an α-amino acid of Groups E and G, and
Y is NH$_2$.

33. A compound of Claim 32, said compound being
MeOSuc-Ala-Ala[C(O)-Ile]Ala-NH$_2$.

34. Compounds of Claim 1 of the formula

R$_1$NHCHR$_2$C(O)X **Is**

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,
R$_1$ is H,
R$_2$ is the residue of an α-amino acid of Groups A, B, E, F or J,
R$_4$ is the residue of an α-amino acid of Groups A, B, C, D, E, F, G or J,
R$_5$ is an α-amino acid of Group E, and
Y is NH$_2$.

35. A compound of Claim 34, said compound being

H-Leu[C(O)Ala]AlaNH$_2$.

36. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ Iu

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,

R$_1$ is P$_2$P$_3$ or P$_2$P$_3$P$_g$, P$_g$ being a Group K protecting group,

P$_2$ is an α-amino acid of Groups E or F,

P$_3$ is an α-amino acid of Groups B, E, F or is deleted,

R$_2$ is H, a residue of α-amino acids of Groups E, F, J, naphthyl, C$_{1-7}$ alkyl, benzyl, phenethyl, or A-SiR$_7$R$_8$R$_9$, R$_7$, R$_8$ and R$_9$ being C$_{1-10}$ alkyl, phenyl, benzyl, phenethyl and A is C$_{1-6}$ alkylene,

R$_3$ is C$_{1-6}$ alkyl, benzyl or phenethyl,

R$_4$ is the residue of an α-amino acid of Groups C, E or H,

R$_5$ is deleted, and

Y is OR$_3$ or NHR$_3$.

37. A compound of claim 36, said compound being

Pg-Val-CHM[C(O)Leu]OCH$_3$.

38. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ Iv

wherein X is -C(O)CHR$_4$C(O)R$_5$Y,

R$_1$ is P$_2$P$_3$P$_4$ or P$_2$P$_3$P$_4$P$_g$, P$_g$ being a Group K protecting group,

P$_2$ is an α-amino acid of Groups C′, E′, F′ and G′,

P$_3$ is an α-amino acid of Groups C′, E′, F′ and G′,

P$_4$ is an α-amino acid of Groups C′, β-Ala, β-Val, or is deleted,

R$_2$ is a residue of an α-amino acid of Groups F′ or E, or cyclohexylmethyl,

R$_3$ is C$_{1-6}$ alkyl, benzyl or phenethyl,

R$_4$ is a residue of an α-amino acid of Group E′ or Val,

R$_5$ is deleted, and

Y is OR$_3$ or NHR$_3$.

39. A compound of Claim 38, said compound being

Thr-Gln-Asn-Tyr-[C(O)Phe]OCH$_3$,

Thr-Gln-Asn-Phe-[C(O)Phe]OCH$_3$,

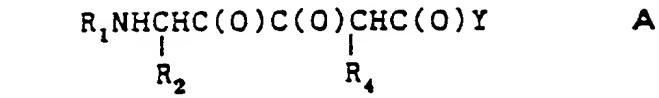
Thr-Leu-Asn-Tyr-[C(O)Phe]NH$_2$,

Thr-Leu-Asn-Phe-[C(O)Phe]OCH$_3$,

Iva-Ser-Asn-Phe-[C(O)Phe]OCH$_3$,

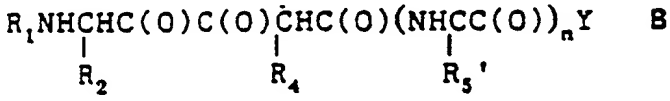
Iva-Ser-Asn-Phe-[C(O)Phe]NH$_2$.

40. A process for preparing compounds of the formulae



A

and



B

the hydrates, isosteres of the pharmaceutically acceptable salts thereof, wherein

R$_1$ is H, an amino protecting group of Group K, an α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group or a peptide comprised of 2 to 4 α-amino acids, the terminal amino acid of which bears a Group K protecting group,

R$_2$ is a residue of an α-amino acid, -A-SiR$_7$R$_8$R$_9$, C$_{1-10}$ alkyl, aralkyl or aryl,

R$_4$ is a residue of an α-amino acid,

R$_5$′ is a residue of an α-amino acid,

n is 1 to 4,

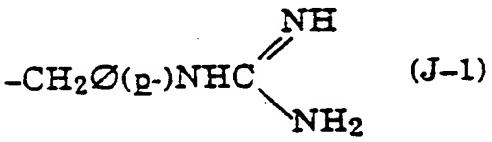
Y is NHR$_3$ or OR$_3$, with

R$_3$ being H, C$_{1-10}$ alkyl, benzyl or phenethyl,

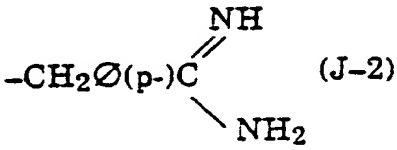
the said protecting groups, α-amino acids or peptide moieties being selected from Groups A, B, C, D, E, F, G, J, C′, E′, F′, G′ and K, said groups being:

A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and their N-methyl derivatives
C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives
D: Pro, Ind
E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, n-Leu and their methyl derivatives
E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and their N-methyl derivatives
F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.
G: Gly, Sar
G′: Gly

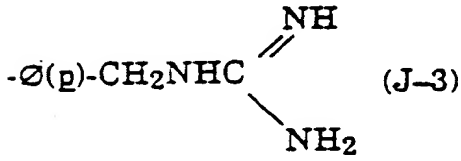
J:



(J–1)

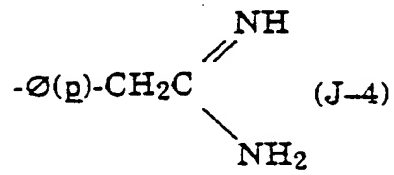


(J–2)



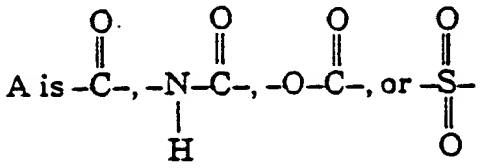
(J–3)

and



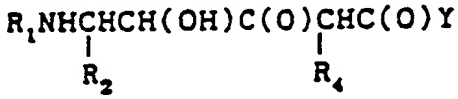
(J–4)

K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′
K′: A-Rz wherein



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro, which comprises

(1) in the instance of preparing compounds of Formula A, the oxidation of a compound of the formula

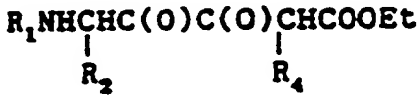


said oxidation being effected with
(a) an *in situ*-formed sulfonium adduct formed by reaction of dimethylsulfoxide with $(CF_3CO)_2O$ or $(COCl)_2$,
(b) a pyridinium dichromate in the presence of glacial acetic acid.

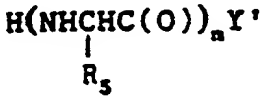
(c) an *in situ* chromic anhydride-pyridine complex, or

(d) 1,1,1-triacetoxy-2,1-benzoxiodol,

(2) in the instance of preparing a compound of Formula B, coupling a compound of the formula



with a compound of the formula



followed by the removal of any Y′ protecting group wherein Y′ is NHR_3' or OR_3, wherein R_3' is a protecting group, C_{1-10} alkyl, benzyl or phenethyl.

41. A compound according to any one of claim I to 40 for use as a pharmaceutically active compound.